The official action of December 5, 2001, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a method for inhibiting neuronal degeneration in the central nervous system or peripheral nervous system of an individual in need thereof by causing NS-specific activated T cells to accumulate at the site of neuronal degeneration in the individual in need. By causing such T cell accumulation at the site of injury or disease, neuronal degeneration at that site is inhibited. The claims exclude the situation where the individual has an autoimmune disease and the T cells are activated against the autoimmune antigen involved in that disease. Preferably, the NS-specific activated T cells are caused to accumulate at the site of neuronal degeneration by administering NS-specific activated T cells (passive immunization) or an NS-specific antigen, a peptide derived therefrom or a nucleotide sequence encoding such an antigen or peptide (active immunization).

It is noted that the examiner has withdrawn the restriction requirement based on the dichotomy between treatment of the CNS and the PNS and, therefore, Groups I-A and II-B have been rejoined. However, the examiner has refused to withdraw the injury/disease dichotomy. It is

further noted that the examiner has rejoined all of the species of activated T cells (Groups Ir, Is and It). Otherwise, the examiner still deems the requirement to be proper and has made it final. This restriction requirement is again respectfully traversed.

In order to clearly establish that the injury/disease dichotomy is not a true dichotomy between patentably distinct inventions, applicants have added new linking claim 38 which is a true generic claim directed toward a method for inhibiting neuronal degeneration, regardless of etiology of that degeneration. Claim 39 specifies that the degeneration results from injury or disease. It is the degeneration which is being treated by all of the embodiments of the present invention and not just the injury or the disease. Furthermore, claim 38 is a true generic claim with respect to the manner of operation of the invention, i.e., it requires that NS-specific activated T cells be caused to accumulate at the site of neuronal degeneration in the individual being treated. It does not matter whether this accumulation is caused by active administration of a NS-specific antigen that causes the NS-specific activated T cells to be generated *in vivo*, or by passive administration of NS-specific activated T cells directly. Accordingly, this linking claim 38 requires that the examiner examine all of the

species of administration that cause the NS-specific activated T cells to accumulate at the site of neuronal degeneration and thereby inhibit any neuronal degeneration, regardless of whether it is originally caused by an injury or a disease.

The language of new claim 38 is supported by the present specification. That the purpose of the administration of a NS-specific antigen is to cause the accumulation of NS-specific activated T cells at the site of neuronal degeneration is supported by the paragraph bridging pages 7 and 8 of the present specification, particularly where it states at page 8, lines 3-6:

> "NS-specific antigen" as used herein refers to an antigen that specifically activates T cells such that following activation, the activated T cells accumulate at a site of injury or disease in the NS of the patient.

See also page 31, lines 1-9, of the present specification. That the passive immunization of the T cells themselves are administered for the same purpose is evident from the paragraph bridging pages 6 and 7 of the specification, particularly page 7, lines 5-9, where it states:

> [T]he T cells of the present invention ... are administered in such a way as to create accumulation of the T cells at the site of injury or disease so as to facilitate neural regeneration or to inhibit neural degeneration.

As to the proviso at the end of claim 38, this is supported in the paragraph bridging pages 6 and 7, where it states:

> If the disease being treated is an autoimmune disease, in which the autoimmune antigen is an NS antigen, the T cells which are used in accordance with the present invention for the treatment of neural damage or degeneration caused by such disease are preferably not activated against the same autoimmune antigen involved in the disease.

Accordingly, claim 38 is fully supported by the present specification. As claim 38 serves as a linking claim, reconsideration and withdrawal of the restriction requirement and action on all the claims now present in the case are, therefore, respectfully urged.

The examiner states that the oath or declaration is defective because the specification to which the declaration is directed has not been adequately identified, noting MPEP §601.01(a). This requirement is respectfully traversed.

The examiner's attention is invited to MPEP [8th Edition], paragraph 602, and particularly the paragraph bridging pages 600-29 and 600-30, where it states:

> Filing dates are granted on applications filed without an oath or declaration in compliance with 37 CFR 1.63, the oath or declaration being filed later with a surcharge. The following combinations of information supplied in an oath or declaration filed after the filing date of the application are acceptable as minimums for identifying a specification and compliance with any one of the items below

> will be accepted as complying with the identification requirement of 37 CFR 1.63:
>
> ...
>
> (E) title of the invention which was on the specification as filed and accompanied by a cover letter accurately identifying the application for which it was intended by either the application number (consisting of the series code and the serial number, e.g., 08/123,456), or serial number and filing date. Absent any statement(s) to the contrary, it will be presumed that the application filed in the USPTO is the application which the inventor(s) executed by signing the oath or declaration.

The declaration forms filed with applicants' cover letter of August 10, 1999, identified the specification to which it applies by the title, "ACTIVATED T-CELLS, NERVOUS SYSTEM-SPECIFIC ANTIGENS AND THEIR USES", as well as by the filing date of the application, 19 May 1999. The cover letter accompanying the declaration, with the heading "LATE SUBMISSION OF FILING FEE AND/OR DECLARATION", specifically identifies the application as serial no. 09/314,161, filed May 19, 1999. Accordingly, this cover letter and the accompanying declaration fully comply with all of the requirements of MPEP §602 in order to identify the specification to which the declaration is directed. Reconsideration and withdrawal of the requirement for a new declaration are, therefore, respectfully urged.

The examiner has objected to the disclosure because the title of the invention is not descriptive. The examiner suggests the following title, "A METHOD FOR REDUCING SECONDARY NEURONAL DEGENERATION BY ADMINISTERING MBP-SPECIFIC ACTIVATED T CELLS". This requirement is respectfully traversed.

It cannot be determined what title will be clearly indicative of the invention to which the claims are directed until a determination is made as to what claims will be examined in light of the new linking claim and applicants' arguments with respect to the restriction requirement. Accordingly, it is respectfully requested that the requirement to submit a new title be held in abeyance until allowable subject matter is indicated in the case, as is permitted by 37 C.F.R. §1.111(b) as this is a requirement as to form not necessary to further consideration of the claims.

Claim 1 has been objected to as the phrase "for ameliorating" should be amended to read "to ameliorate". Claim 1 has now been amended as suggested by the examiner, thus obviating this objection.

The examiner objects to claims 1, 2 and 19 as reciting non-elected species.

In view of the presence of linking claim 38, it is believed that all of the species within claims 1, 2 and 19 will have to be examined once the elected species are found to

be allowable. Furthermore, the recitation of non-elected species is not a grounds for objection. If the elected species can be rejected, then the claims must be rejected on the same grounds. If the elected species is not rejected, then the claim must either be examined in its full scope or some type of improper Markush group rejection be made. In any event, withdrawal of this objection pending resolution of the arguments regarding linking claim 38 is respectfully urged.

Claims 1 and 2 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3 and 16 of co-pending application no. 09/218,277. The examiner states that a timely filed terminal disclaimer in compliance with 37 C.F.R. §1.321(c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground, provided the conflicting application or patent or application is shown to be commonly owned with this application.

If at the time allowable claims are indicated in the present application and in application 09/218,277, those claims are still obvious over one another, then applicants will file a terminal disclaimer in order to obviate this requirement. It is possible, however, that in the course of prosecution the claims will be amended so as to avoid this

rejection. Accordingly, it is requested that this requirement be held in abeyance until allowable subject matter is found in one or both of the cases in question.

Claims 1, 2, 4-8, 16 and 19 have been rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for a method of reducing secondary neuronal degeneration in the central nervous system or peripheral nervous system to ameliorate the degenerative effects of spinal cord injury or blunt trauma, by administering to an individual in need thereof a composition consisting of activated T cells sensitized to myelin basic protein (MBP), wherein the MBP-activated T cells reduce secondary neuronal degeneration, it does not reasonably provide enablement for a method of preventing or inhibiting neuronal degeneration in the central nervous system or peripheral nervous system for ameliorating the effects of injury or disease, by administering to an individual in need thereof at least one active ingredient selected from the group consisting of NS-specific activated T cells, a NS-specific antigen, a peptide derived from a NS-specific antigen, a nucleotide sequence encoding a NS-specific antigen, and a nucleotide sequence encoding a peptide derived from a NS-specific antigen. The examiner states that the terms "preventing" and "inhibiting" are interpreted as meaning that

an activity will not occur, i.e., neuronal degeneration will not occur. The examiner states that undue experimentation would be required of the skilled artisan to determine the quantity of MBP-specific activated T cells administered, the best route of administration, the duration of treatment, and possible side effects to completely prevent and inhibit neuronal degeneration in the CNS or PNS. The examiner states that the specification does not teach use of other NS-specific activated T cells other than MBP-specific activated T cells particularly in view of the fact that OVA-specific and p277-specific T cells do not reduce secondary neuronal degeneration in retinas. The examiner concludes that undue experimentation would be required to sensitize T cells to every nervous system antigen and administer the cells to an individual to reduce neuronal degeneration. The examiner also questions the oral administration, as in claim 16. This rejection is respectfully traversed.

First, it is respectfully pointed out that the examiner is incorrect in interpreting the terms "preventing" and "inhibiting" as being synonymous. If they were intended to have been synonymous, they would not have both been used. "Preventing" means that the activity is prevented from occurring, at least to some extent. "Inhibiting" means only to restrain or to hinder, but not necessarily to completely

stop all activity. If an activity is inhibited, that means that it is decreased. When activity, such as secondary neuronal degeneration, is prevented, that means at least some of the degeneration which would have otherwise occurred is prevented from happening. Even that does not mean that no activity will occur at all. The claims call for amelioration of a condition, not complete cure. Thus, the examiner's comments about the amount of experimentation necessary to *completely* prevent neuronal degeneration misses the point as the claims to not require this.

With respect to the examiner's statement that the specification does not teach reducing secondary neuronal degeneration by administration of any other NS-specific activated T cells other than MPB-activated T cells, this is also not entirely correct. Example 8.1 refers to administration of MOG, which is another NS-specific antigen which causes NS-specific activated T cells to accumulate at the site of injury. It was shown to work as well as MBP, and this further supports the credibility of the statements in the present specification that any NS-specific antigen will serve to activate the T cells. The fact that OVA-specific and p277-specific T cells do not reduce secondary neuronal degeneration is in complete accordance with the statements of the present specification as these are controls that are not NS-specific.

It would not take undue experimentation to determine what other NS-specific antigens could be used to activate T cells as there is no reason for one of ordinary skill in the art reading the present specification to believe that any such antigen will not be operable. Many examples are given, such as at page 31, lines 18-21. Experiments were conducted with two of these examples, MBP and MOG, proving their operability. The specification further states at the last sentence of page 32 that the crucial test is that the antigen used for activating T cells causes the T cells to be capable of recognizing an antigen in the NS of the mammal being treated. The experimentation to confirm that any given NS-specific antigen meets this test would not involve undue experimentation.

The examiner has not provided any reasons why one of ordinary skill in the art, reading the present specification as a whole, would consider applicants' statements that the invention is applicable to the use of any NS-specific antigen would be incredible. Without such specific reasoning on the part of the examiner, statements in the present specification must be accepted as true, see MPEP §2164.04. Furthermore, since the rejection appears to be based on the examiner's holding that the statements in the present specification are

incredible, this is really in the nature of a utility rejection, see MPEP §2164.07(a). As stated in MPEP §2164.07B:

> The examiner has the initial burden of challenging an asserted utility. Only after the examiner has provided evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince one of ordinary skill in the art of the invention's asserted utility.

No experimentation is necessary to practice this invention as all NS-specific antigens would be expected to be operable to activate T cells for use in the present invention.

With respect to oral administration, the examiner's attention is invited to Example 9, which shows an experiment involving oral administration. In any event, claim 16 is now directed specifically to the administration of peptide, rather than the administration of T cells.

As a large quantity of experimentation is not necessary to prevent or inhibit neuronal degeneration by NS-specific activated T cells, the present rejection must be withdrawn. Reconsideration and withdrawal of this rejection are, therefore, respectfully urged.

Claims 1, 2, 4-8, 16 and 19 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Regarding claims 1, 2, 4-8 and 16, the examiner states that the acronyms "NS" and "HLA" render the claims vague and

indefinite and that abbreviations should be spelled out in all independent claims for clarity.

The first appearance of these terms has now been spelled out as suggested by the examiner, thus obviating this part of the rejection.

The examiner states that claims 1, 2, 4-8, 16 and 19 are indefinite as not having a step that clearly relates back to the preamble, such as indicating that the active ingredient prevents or inhibits neuronal degeneration in the central nervous system or peripheral nervous system. The examiner states that in claim 19 there is no step indicating that the activated T cells banked for future use will inhibit or prevent neuronal degeneration.

Claim 1 has now been amended to insert such a statement. Claim 19 has been amended to remove from the preamble the statement of what the T cells will eventually be used for. Such a statement is not necessary in a process claim drawn to a process of making. Accordingly, this part of the rejection is no longer applicable to claim 19 as presently amended.

The examiner states that the term "effects" in claims 1, 2, 4-8, 16 and 19 is a relative term that renders the claim indefinite. The examiner states that this issue

could be overcome by amending the claims to recite "degenerative effects", rather than "effects".

Claim 1 has now been amended in the manner suggested by the examiner, thus obviating this part of the rejection.

The examiner states that claim 16 recites a limitation "said composition", but there is no antecedent basis therefor.

Claim 16 has now been amended so as to depend from claim 13 and to refer to "said NS-specific antigen or peptide" as is clearly present in claim 13. Thus, this portion of the rejection is no longer applicable to claim 16 as amended.

The examiner states that the term "actively immunized" in claim 16 is a relative term that renders the claims indefinite.

It is believed that it is a term of art that immunization with an antigen is considered "active" immunization, while administration of T cells or antibodies themselves is considered "passive" immunization. In any event, claims 16 has now been amended to delete the term "actively immunized" so as to avoid this part of the rejection.

Accordingly, reconsideration and withdrawal of the entire rejection under 35 U.S.C. §112, second paragraph, are respectfully urged.

Claims 1, 4-6, 8 and 19 have been rejected under 35 U.S.C. §102(b) as being anticipated by Popovich. The examiner states that Popovich teaches the intravenous administration of MBP-activated T cells into naïve recipient rats. The T cells are cultured with MBP *in vitro* before being injected into the recipient animals. This rejection is respectfully traversed.

The examiner concedes that the MBP-activated T cells are only administered to naïve recipient rats, meaning that the rats do not have any disease or injury. Claim 1 requires that the T cells be administered to an individual in need of prevention or inhibition of neural degeneration to ameliorate the degenerative effects of injury or disease. As the mice of Popovich have no such injury or disease, they are not in need of prevention or inhibition of neuronal degeneration, and therefore, claims 1, 4-6 and 8 cannot be anticipated thereby. With respect to claim 19, this claim has been amended to specify that the activated T cells must be stored in a cell bank of T cells that have been activated against nervous system antigen. The cells of Popovich are not stored in a cell bank and, thus, claim 19 is not anticipated. Reconsideration and withdrawal of this rejection are, therefore, also respectfully urged.

The art made of record and not relied upon has been noted, as has the examiner's implicit recognition they are

insufficiently pertinent to warrant their application against the claims.

It is submitted that all the claims now present in the case clearly define over the references of record. Reconsideration and allowance are, therefore, earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made".

Respectfully submitted,

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Version with Markings to Show Changes Made

In the Specification

The paragraph on page 9, beginning at line 5, has been amended as follows:

In another embodiment, cell~~,~~ banks can be established to store NS sensitized T cells for neuroprotective treatment of individuals at a later time, as needed. In this case, autologous T cells may be obtained from an individual. Alternatively, allogeneic or semi-allogeneic T cells may be stored such that a bank of T cells of each of the most common MHC-class II types are present. In case an individual is to be treated for an injury, preferably autologous stored T cells are used, but, if autologous T cells are not available, then cells should be used which share an MHC type II molecule with the patient, and these would be expected to be operable in that individual. The cells are preferably stored in an activated state after exposure to an NS antigen or peptide derived therefrom. However, the cells may also be stored in a resting state and activated once they are thawed and prepared for use. The cell lines of the bank are preferably cryopreserved. The cell lines are prepared in any way which is well known in the art. Once the cells are thawed, they are preferably cultured prior to injection in order to eliminate non-viable cells. During this culturing, the cells can be

activated or reactivated using the same NS antigen or peptide as used in the original activation. Alternatively, activation may be achieved by culturing in the presence of a mitogen, such as phytohemagglutinin (PHA) or concanavalin A (~~prefereably~~preferably the former). This will place the cells into an even higher state of activation. The few days that it takes to culture the cells should not be detrimental to the patient as the treatment in accordance with the present invention may occur any time up to a week or more after the injury in order to still be effective. Alternatively, if time is of the essence, the stored cells may be administered immediately after thawing.

The paragraph on page 32, beginning at line 8, has been amended as follows:

~~an~~ An NS-specific antigen may be obtained by an NS biopsy or necropsy from a mammal including, but not limited to, from a site of CNS injury; from cadavers; or from cell lines grown in culture. Additionally, an NS-specific antigen may be a protein obtained by genetic engineering, chemically synthesized, etc.

The paragraph on page 32, beginning at line 14, has been amended as follows:

In addition to NS-specific antigens, the invention also relates to peptides derived from NS-specific antigens or derivatives including chemical derivatives and analogs of NS-specific antigens which are functionally active, i.e., they are capable of displaying one or more ~~know~~ known functional activities associated with a full-length NS-specific antigen. Such functional activities include, but are not limited to, antigenicity (ability to bind (or compete with an NS-antigen for binding) to an anti-NS-specific antibody), immunogenicity (ability to generate antibody which binds to an NS-specific protein), and ability to interact with T cells, resulting in activation comparable to that obtained using the corresponding full-length antigen. The crucial test is that the antigen which is used for activating the T cells causes the T cells to be capable of recognizing an antigen in the NS of the mammal (patient) being treated.

In the Claims

Claims 1, 4, 16 and 19 have been amended as follows:

1 (Amended). A method for preventing or inhibiting neuronal degeneration in the central nervous system or peripheral nervous system ~~for ameliorating~~to ameliorate the degenerative effects of injury or disease, comprising administering to an individual in need thereof at least one

active ingredient selected from the group consisting of nervous system (NS)-specific activated T cells; a NS-specific antigen; a peptide derived from a NS-specific antigen; a nucleotide sequence encoding a NS-specific antigen; and a nucleotide sequence encoding a peptide derived from a NS-specific antigen, thereby causing NS-specific activated T cells to accumulate at the site of injury or disease and prevent or inhibit neuronal degeneration at that site, with the proviso that when the disease being ameliorated is an autoimmune disease, the NS-specific antigen is not an autoimmune antigen involved in that disease and said T cells are not activated against an autoimmune antigen involved in that disease.

4 (Amended). The method according to claim 1 wherein said NS-specific activated T cells are selected from the group consisting of autologous T cells, allogeneic T cells from related donors, and human lymphocyte antigen (HLA)-matched or partially matched semi-allogeneic or fully allogeneic donors.

16 (Amended). The method according to claim ~~1~~ 13, wherein said ~~composition~~ NS-specific antigen or peptide is administered orally ~~and the individual is actively immunized~~so as to build up a critical T cell response.

19 (Amended). A method for providing T cells for ~~inhibiting or preventing neuronal degeneration in the central~~

~~nervous system or peripheral nervous system for ameliorating the effects of injury or disease~~future use, comprising:

obtaining T cells from an individual;

activating said T cells against at least one nervous system antigen; and

~~banking~~ storing said activated T cells in a cell bank of T cells that have been activated against a nervous system antigen, for future use.

Claims 38-40 have been added.